FORM PTO-1390 (REV 5-93)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY DOCKET NO. 108907-00024
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		DATE: January 9, 2002
		U.S. APPLN. NO. (IF KNOWN, SEE 37 C.F.R. 1.5) 10/019316
INTERNATIONAL APPLICATION NO. PCT/EP00/05722	INTERNATIONAL FILING DATE 21 June 2000	PRIORITY DATE CLAIMED 9 July 1999

TITLE OF INVENTION: A PROCESS FOR OBTAINING (NITROXYMETHYL)PHENYL ESTERS OF SALICYLIC ACID DERIVATIVES

APPLICANT(S) FOR DO/EO/US: Graziano CASTALDI; Erminio OLDANI; Gabriele RAZZETTI; and Francesca BENEDINI

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
(THE BASIC FILING FEE IS ATTACHED)

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This express request to begin national examination procedures [35 U.S.C. 371(f)] at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper demand for International Preliminary Amendment was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed [35 U.S.C. 371(c)(2)]
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☒ A translation of the International Application into English [35 U.S.C. 371(c)(2)].

7. ☐ Amendments to the claims of the International Application under PCT Article 19 [35 U.S.C. 371(c)(3)]
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)].

9. ☒ An oath or declaration of the inventor(s) [35 U.S.C. 371(c)(4)].

10. ☒ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 [35 U.S.C. 371(c)(5)].

Items 11 - 16 below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.

12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information: CHECK NO. 332485; Form PCT/ISA/210; Form PCT/IPEA/416; Form PCT/IPEA/409

U.S. APPLN. NO. (IF KNOWN, SEE 37 C.F.R. 1.5) 10/019316	INTERNATIONAL APPLICATION NO. PCT/EP00/05722	ATTORNEY DOCKET NO. 108907-00024 DATE: January 9, 2002

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee [37 C.F.R. 1.492(a)(1)-(5)]: Search Report has been prepared by the EPO or JPO.....$890.00 International preliminary examination fee paid to USPTO (37 C.F.R. 1.482).....$710.00 No international preliminary examination fee paid to USPTO (37 C.F.R. 1.482) but international search fee paid to USPTO [37 C.F.R. 1.445(a)(2)].....$740.00 Neither international preliminary examination fee (37 C.F.R. 1.482) or international search fee [37 C.F.R. 1.445(a)(2)] paid to USPTO.....$1,040.00 International preliminary examination fee paid to USPTO (37 C.F.R. 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$ 100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date [37 C.F.R. 1.492(e)].		

Claims	Number Filed	Number Extra	Rate		
Total Claims	7 - 20 =	0	X $ 18.00		
Independent Claims	1 - 3 =	0	X $ 84.00		
Multiple dependent claim(s) (if applicable)			+ $280.00		
TOTAL OF ABOVE CALCULATIONS =				$ 890.00	
Reduction by one-half for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 C.F.R. 1.9, 1.27, 1.28).					
SUBTOTAL =				$ 890.00	
Processing fee of $130.00 for furnishing the English translation later the ☐ 20 ☐ 30 months from the earliest claimed priority date [37 C.F.R. 1.492(f)]. +					
TOTAL NATIONAL FEE =				$ 890.00	
Fee for recording the enclosed assignment [37 C.F.R. 1.21(h)]. The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. 3.28, 3.31). $40.00 per property +				$ 40.00	
TOTAL FEES ENCLOSED =				$ 930.00	
				Amount to be refunded	$
				Charged	$

a. ☒ A check in the amount of $930.00 to cover the above fees is enclosed.
b. ☐ Please charge my Deposit Account No. 01-2300 in the amount of $ to cover the above fee.
A duplicate copy of this sheet is enclosed.
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 01-2300.

NOTE: Where an appropriate time limit under 37 C.F.R. 1.494 or 1.495 has not been met, a petition to revive [37 C.F.R. 1.137(a) or (b)] must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
Customer No. 004372
Arent Fox Kintner Plotkin & Kahn
1050 Connecticut Avenue, N.W., Suite 400
Washington, D.C. 20036-5339
Tel: (202) 857-6000 Fax: (202) 638-4810

Douglas H. Goldhush
Reg. No. 33,125

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

CASTALDI et al — Group Art Unit: Not yet assigned

International Appln. No.: PCT/EP00/05722 — Examiner: Not yet assigned

Filed: January 9, 2002 — Attorney Dkt. No.: 108907-00024

For: A PROCESS FOR OBTAINING (NITROXYMETHYL)PHENYL ESTERS OF SALICYLIC ACID DERIVATIVES

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

January 9, 2002

Sir:

Prior to calculation of the filing fees and initial examination of the application, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend claims 3 and 4 as follows. A copy of the marked up original claims is attached to this response showing the changes as set forth in amended 37 CFR 1.121.

3. (Amended) A process according to claim 1, wherein in step a) the organic solvents are C_1-C_4 aliphatic alcohols; aromatic hydrocarbons, aliphatic esters, chlorinated organic solvents, aliphatic and cycloaliphatic ketones.

4. (Amended) A process according to claim 1, wherein in step a) the reaction is carried out at a temperature in the range -20°C and +50°C by using, with respect to the hydroxybenzylalcohol moles under reaction, an amount by moles respectively of acid halide (I-A) in the range between 1 and 2, preferably between 1.2 and 1.5 and an amount by moles of base in the range between 0.1 and 2, preferably between 0.5 and 2.

REMARKS

Claims 1-7 are pending in this application. By this Amendment, claims 3 and 4 are amended to correct the multiple dependencies thereof and to place this application into better condition for examination. No new matter has been added.

In the event that there are any fees due with respect to the filing of this paper, please charge Deposit Account No. 01-2300.

Respectfully submitted,

Douglas H. Goldhush
Registration No. 33,125

Customer No. 004372
ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
1050 Connecticut Avenue, N.W.,
Suite 400
Washington, D.C. 20036-5339
Tel: (202) 857-6000
Fax: (202) 638-4810

DHG:scc

Enclosure: Marked-up Copy of Amended Claims

MARKED-UP COPY OF AMENDED CLAIMS 3 AND 4
ATTY. DOCKET NO. 108907-00024

3. (Amended) A process according to [claims 1-2] claim 1, wherein in step a) the organic solvents are C_1-C_4 aliphatic alcohols; aromatic hydrocarbons, aliphatic esters, chlorinated organic solvents, aliphatic and cycloaliphatic ketones.

4. (Amended) A process according to [claims from 1 to 3] claim 1, wherein in step a) the reaction is carried out at a temperature in the range -20°C and +50°C by using, with respect to the hydroxybenzylalcohol moles under reaction, an amount by moles respectively of acid halide (I-A) in the range between 1 and 2, preferably between 1.2 and 1.5 and an amount by moles of base in the range between 0.1 and 2, preferably between 0.5 and 2.

A PROCESS FOR OBTAINING (NITROXYMETHYL)PHENYL ESTERS OF SALICYLIC ACID DERIVATIVES.

* * * *

The present invention relates to a process for obtaining (nitroxymethyl)phenyl esters of salicylic acid derivatives.

It is known in the prior art that the (nitroxymethyl)phenyl esters of the salicylic acid derivatives can be prepared by various synthesis processes. In the patent application WO 97/16405 the reaction of the acyl chloride of the acetylsalicylic acid with (nitroxymethyl)phenol is described. The (nitroxymethyl) phenol is prepared by a synthesis which comprises the following steps:

- reaction of the phenol with HBr in organic solvent to obtain (bromomethyl)phenol, and
- reaction of the (bromomethyl) phenol in organic solvent with $AgNO_3$ with formation of (nitroxymethyl)phenol.

The process based on the reaction between (nitroxymethyl) phenol and the acyl chloride of the acetylsalicylic acid shows the following drawbacks:

- the (bromomethyl)phenol obtained in the first synthesis step is a chemically unstable and irritating compound;
- the nitrating agent used in the reaction with (bromomethyl)phenol is a very expensive reactant;
- the (nitroxymethyl)phenol is an unstable compound, which can easily decompose in an uncontrollable way; and it must be purified before the reaction with the acetylsalicylic acid chloride, furtherly increasing the production costs and requiring supplementary units in the production plant.

In conclusion the synthesis of above derivatives, by using the intermediate (nitroxymethyl) phenol, is difficult and expensive to be carried out on an industrial scale.

In PCT Patent EP 00/00353 in the name of the Applicant a

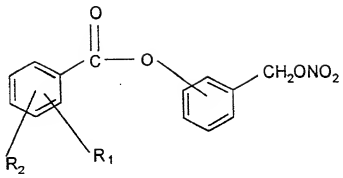
synthesis process of nitroxy derivatives of formula (I) (see hereunder) is described, by submitting to nitration with $AgNO_3$ (hydroxymethyl) phenyl esters of the acetylsalicylic acid, obtained by reacting the acid chloride with hydroxybenzaldehyde and reducing the aldehydic group to primary alcohol. Also this process, as the above mentioned uses silver nitrate as nitrating agent and therefore it is not much advantageous from an industrial point of view. Besides the process global yields are not high.

By using the teaching of the prior art, it is possible to obtain the salicylic acid nitroxyderivatives of formula (I) (see below) by reacting a (hydroxymethyl)phenyl ester of the acetylsalicylic acid with nitrating reactants based on nitric acid. However under the reaction conditions of the prior art the nitric acid produces undesired reactions, such as for example the nitration of aromatic substrata (ref. "Nitration: Methods and Mechanism", 1984 VCH ed., p. 269) and the oxidation of primary alcohols to aldehydes (ref. "Industrial and Laboratory Nitration" 1976 ACS publ., p. 156).

Therefore also said processes of the prior art are unable to solve the problem of the preparation on industrial scale of the nitroxyderivatives of the salicylic acid as above defined.

The need was felt to prepare nitroxy derivatives of (hydroxymethyl)phenyl esters of the acetylsalicylic acid by a process cheaper than those of the prior art both for the nitrating agent used and for the yields, and substantially without the drawbacks of the prior art.

An object of the present invention is a process for obtaining (nitroxymethyl)phenyl esters of the salicylic acid derivatives, compounds having the following formula (I):



(I)

wherein:

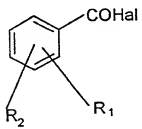
R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3-C_5 alkyl, or the residue of a saturated heterocyclic ring having 5 or 6 atoms, containing hetero-atoms independently selected between O and N;

R_2 is hydrogen, halogen, linear or branched when possible C_1-C_4 alkyl, linear or branched when possible C_1-C_4 alkoxyl; linear or branched when possible C_1-C_4 perfluoroalkyl, for example trifluoromethyl; mono- or di- (C_1-C_4)alkylamino;

preferably in (I) R_1 is acetoxy and is in ortho position with respect to the carboxylic group, R_2 is hydrogen; the oxygen of the ester group is bound to the aromatic ring substituted with the (nitroxy)methylene group in ortho, meta or para position with respect to the (nitroxy)methylene group; preferably the position is the meta one;

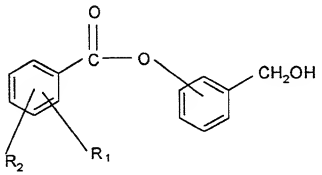
said process comprising the following steps:

a) reaction of a halide of a salicylic acid derivative of formula (I-A):



(I-A)

wherein Hal = Cl, Br, and R_1 and R_2 have the above indicated meaning, with hydroxybenzylalcohol in the presence of a base, in an organic solvent, or in a mixture of water with a miscible or immiscible organic solvent with water, to give the compound (I-B) having the following formula:



(I-B)

wherein R_1 and R_2 are as above defined;

b) nitration of the compound (I-B) in anhydrous conditions, in an inert organic solvent, by a mixture formed by steaming nitric acid with an inorganic acid different from nitric acid or with an organic acid, or with the anhydride of one or two organic acids, to give the nitroxyderivative of formula (I).

c) recovery of the final product by adding water to the organic phase, separating the phases, drying and evaporating the organic phase.

In step a) the base can be an inorganic base, such as for example hydroxides, oxides, carbonates and bicarbonates of alkaline metals (sodium, potassium, lithium); or an organic base, for example a tertiary amine, for example aliphatic, cycloaliphatic, heterocyclic, heterocyclic aromatic, such as triethylamine, diisopropyl-ethylamine, N-methylmorpholine, diazaabicyclooctane, etc.

The organic solvent used in step a) can be an organic solvent miscible with water such as C_1-C_4 aliphatic alcohols, for example methanol, ethanol, isopropanol, n-butanol; or an

organic solvent immiscible with water for example aromatic hydrocarbons such as toluene and xylene, chlorinated organic solvents such as methylene chloride, chlorobenzene, other solvents which can be used are aliphatic esters for example of C_1-C_4 acids with C_1-C_5 alcohols such as for example ethyl acetate and butyl acetate, etc.: aliphatic and cycloaliphatic ketones, such as C_3-C_{12} for example acetone, methylketone, cyclohexanone, etc.

In step a) the reaction is carried out at a temperature in the range -20°C and +50°C, preferably 0°C-20°C, by using, with respect to the hydroxybenzylalcohol moles under reaction, an amount by moles of acid halide (I-A) in a ratio between 1 and 2, preferably between 1.2 and 1.5, and an amount by moles of base between 0.1 and 2, preferably between and 2.

The compound I-B) is recovered from the reaction mixture by addition of water and optionally, when the reaction takes place in an aqueous solvent or in a mixture of water with an hydrosoluble organic solvent, by addition of an organic solvent immiscible with water, such as ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried, evaporated and the product is recovered. If necessary, the compound can be purified by crystallization from solvents such as for example n-hexane, n-heptane, ligroin, toluene, methanol, isopropanol, diisopropylether, etc or their mixtures. Generally the yields are higher than 80%.

In step b) the nitration reaction is carried out at a temperature in the range -20°C and +40°C, preferably from 0°C to 20°C; the used amount by moles of nitric acid is in a ratio between 1 and 6, preferably 1 and 3, with respect to the moles of the hydroxyester (I-B); the amount by moles of organic or inorganic acid different from nitric acid, or of anhydride as above defined, is in a ratio comprised betwenn 0.5 and 6, preferably between 1 and 3 with respect to the moles of the compound (I-B).

The inorganic acid different from nitric acid is for example sulphuric acid; the organic acid is for example methansulphonic acid, trifluoromethansulphonic acid, trifluoroacetic acid, trichloroacetic acid, acetic acid; the organic

acid anhydride is for example acetic anhydride, trifluoromethansulphonic anhydride, trifluoroacetic anhydride, trichloroacetic anhydride, etc., or mixed anhydrides such as for example trifluoroacetic-trifluoromethansulphonic anhydride, etc.

The inert organic solvent used in step b) is a solvent which has boiling point lower than 200°C at atmospheric pressure and it can be a chlorinated solvent, such as for example dichloromethane; or a nitroalkane such as for example nitromethane, or an aliphatic or cycloaliphatic ether such as for example methylterbutylether, tetrahydrofuran, etc.; an ester for example ethyl acetate; or an aliphatic or aromatic nitrile such as for example acetonitrile, benzonitrile.

The solvent volume is not critical, generally the volume is comprised betwen 1 and 20 times with respect to the amount by weight of hydroxyester (I-B) under reaction.

When the nitration in step b) is carried out in the presence of an organic anhydride as above defined, preferably the anhydride is first mixed with the hydroxyester (I-B) and then the resulting mixture is added to the nitric acid solution in the inert organic solvent.

Preferably the used organic anhydride is acetic anhydride.

In step c) it is possible to recrystallize the obtained compound by using solvents such as for example n-hexane, n-heptane, ligroin, methanol, isopropanol or their mixtures.

The following Examples describe the invention without limiting the scope thereof.

EXAMPLE 1a

Preparation of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (compound I-B) in admixture water-organic solvent

3-hydroxymethylphenol (25.25 g, 0.2 moles) is dissolved in a 5% hydroxide sodium solution (160 ml). To the so obtained solution an acetylsalicylic acid chloride solution (40.4 g, 0.2 moles) in dichloromethane (50 ml) is added at room temperature, under stirring. The mixture is maintained at room temperature under stirring for 2 hours and then extracted with dichloromethane (2 x 100 ml). The organic phase is separated,

anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from a mixture of ethyl acetate and hexane. 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (45.8 g, 0.16 moles, yield 80%) is obtained.

M.P.: 79°-81°C.

^{1}H NMR($CDCl_3$) δ (ppm): 2.29 (s, 3H); 4.71 (s, 2H); 7.07-8.2 (m, aromatics, 8H).

EXAMPLE 1b

Preparation of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (compound I-B) in organic solvent immiscible with water

3-hydroxymethylphenol (10 g, 0.08 moles) is dissolved in toluene (50 ml) containing triethylamine (9.8 g, 0.1 moles). To the so obtained solution an acetylsalicylic acid chloride solution (16 g, 0.08 moles) in toluene (50 ml) is added at a temperature of 5°-10°C under stirring. The mixture is maintained at a temperature in the above mentioned range, under stirring for 2 hours, then poured in water and then extracted with dichloromethane (2 x 100 ml). The organic phase is separated, washed in sequence with a 25% w/v potassium carbonate solution, with water, with a 3% hydrochloric acid solution and lastly with water again, then anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol. 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (45.8 g, 0.16 moles, yield 80%) is obtained.

M.P.: 79°-81°C.

^{1}H NMR($CDCl_3$) δ (ppm): 2.29 (s, 3H); 4.71 (s, 2H); 7.07-8.2 (m, aromatics, 8H).

EXAMPLE 1c

Preparation of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (compound I-B) in organic solvent miscible with water

3-hydroxymethylphenol (10 g, 0.08 moles) is dissolved in acetone (50 ml). In the obtained solution potassium carbonate in powder (22.2 g, 0.16 moles) is suspended. To the suspension

an acetylsalicylic acid chloride solution (16 g, 0.08 moles) in acetone (50 ml) is added at a temperature of 5°-10°C, under stirring. The mixture is maintained at a temperature in the above mentioned range, under stirring, for 2 hours, then filtered and the solvent evaporated under vacuum. The residue is crystallized from isopropanol. 3-hydroxymethylphenyl ester of the 2-acetoxy-benzoic acid (21.0 g, 0.07 moles, yield 91%) is obtained.

M.P.: 79°-81°C.

^{1}H NMR($CDCl_3$) δ (ppm): 2.29 (s, 3H); 4.71 (s, 2H); 7.07-8.2 (m, aromatics, 8H).

EXAMPLE 2

Preparation of 3-nitroxymethylphenyl ester of the 2-acetoxy-benzoic acid by nitration with steaming nitric acid, in the presence of sulphuric acid, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid.

A solution of steaming nitric acid (3.92 g, 62.2 mmoles, 3 moles with respect to the moles of the hydroxyester I-B) and sulphuric acid 96% (6.10 g, 62.2 mmoles, 3 moles with respect to the moles of the hydroxyester 1-B) in dichloromethane (25 ml) is cooled at 0°C and added in 1 hour, under stirring and in nitrogen atmosphere, with a 3-hydroxymethylphenyl ester solution of the 2-acetoxybenzoic acid (6 g, 20.7 mmoles) in 25 ml of dichloromethane. The mixture is then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol obtaining the 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (5.6 g, 17 mmoles, yield 82%).

M.P.: 61°-62°C.

^{1}H NMR($CDCl_3$) δ (ppm): 2.31 (s, 3H); 5.44 (s, 2H); 7.16-8.22 (m, aromatics, 8H).

EXAMPLES 2a-2f

Example 2 was repeated by varying the moles of nitric acid and of sulphuric acid with respect to the moles of the intermediate 3-hydroxymethylphenyl ester of the 2-

acetoxybenzoic acid (I-B). In the following Table 1 the molar ratios of the used reactants with respect to the compound I-B and the relative per cent ratio between the 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (I), the 3-(formyl)phenyl ester of the 2-acetoxybenzoic acid (I-B1) are reported, considering, when present, also the starting compound (I-B).

The Table shows that the highest yield is obtained by using the molar ratio nitric acid/compound (I-B) equal to 3 and sulphuric acid/compound (I-B) equal to 1.5.

Table 1

Example	Moles HNO_3/I-B	Eq. H_2SO_4/I-B	Moles H_2SO_4/I-B	Relative Ratio %		
				(I)	(I-B)	(I-B1)
a	2	0	0	5	15	80
b	2	1	0.5	25	0	75
c	1	1	0.5	54	0	46
d	1	0.5	0.25	5	14	55
e	2	2	1	69	0	31
f	3	3	1.5	99	0	1

EXAMPLE 3

Preparation of 3-nitroxymethylphenil ester of the 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the

presence of acetic anhydride, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid.

A solution of steaming nitric acid (1.44 g, 22.8 mmoles), acetic anhydride, (2.33 g, 22.8 mmoles) in dichloromethane (25 ml) is cooled at 0°C and under stirring added in 1 hour, in nitrogen atmosphere, with a 3-hydroxymethylphenyl ester solution of the 2-acetoxybenzoic acid (6 g, 20.7 mmoles) in 25 ml of dichloromethane. The mixture is heated up to 20°C in one hour and then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol and 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (5.6 g, 17 mmoles, yield 82%) is obtained.

EXAMPLE 4

Preparation of 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the presence of acetic anhydride, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (acetic anhydride mixed with hydroxyester).

A solution of steaming nitric acid (1.44 g, 22.8 mmoles), in dichloromethane (25 ml) is cooled at 0°C and added in 1 hour, under stirring and in nitrogen atmosphere, with a solution of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (6 g, 20.7 mmoles) and acetic anhydride (2.33 g, 22.8 mmoles) in 25 ml of dichloromethane. The mixture is heated up to 20°C in one hour and then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydrified with sodium shulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol to give 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (6.42 g, 19.5 mmoles, yield 94%).

EXAMPLE 5

Preparation of 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the presence of methansulphonic acid, of 3-hydroxymethylphenyl

ester of the 2-acetoxybenzoic acid.

A steaming nitric acid solution (1.44 g, 22.8 mmoles) and methansulphonic acid (2.55 g, 22.8 mmoles) in dichloromethane (25 ml) is cooled at 0°C and under stirring added in 1 hour, in nitrogen atmosphere, with a 3-hydroxymethylphenyl ester solution of the 2-acetoxybenzoic acid (6 g, 20.7 mmoles) in 25 ml of dichloromethane. The mixture is diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol to give 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (2.73 g, 8.29 mmoles, yield 40%).

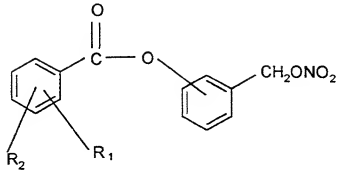
EXAMPLE 6

Preparation of 3-nitroxymethylphenyl ester of 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the presence of acetic anhydride, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid.

A steaming nitric acid solution (990 mg, 15.2 mmoles), acetic anhydride (1.55 g, 15.2 mmoles) in dichloromethane (25 ml) is cooled at 0°C and, under stirring, added in 1 hour, under nitrogen atmosphere, with a solution of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (4 g, 13.8 mmoles) in 25 ml of dichloromethane. The mixture is heated in one hour up to 20°C and then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol to give 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (4.1 g, 12.28 mmoles, yield 89%).

CLAIMS

1. A process for obtaining compounds of formula (I):



(I)

wherein:

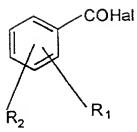
R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3-C_5 alkyl or the residue of a saturated heterocyclic ring having 5 or 6 atoms, containing heteroatoms independently selected between O and N;

R_2 is hydrogen, halogen, linear or branched when possible C_1-C_4 alkyl, linear or branched when possible C_1-C_4 alkoxyl; linear or branched when possible C_1-C_4 perfluoroalkyl; mono- or di- (C_1-C_4) alkylamino;

preferably in (I) R_1 is acetoxy and it is in ortho position with respect to the carboxylic group, R_2 is hydrogen; the oxygen of the ester group is bound to the aromatic ring substituted with the (nitroxy)methylene group in ortho, meta or para position with respect to the (nitroxy)methylene group; preferably the position is the meta one;

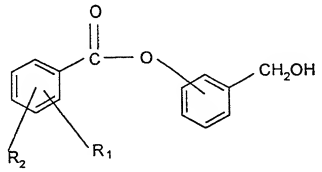
said process comprising the following steps:

a) reaction between an halide of a salicylic acid derivative of formula (I-A)



(I-A)

wherein Hal = Cl, Br, and R_1 and R_2 have the above indicated meaning, with hydroxybenzylalcohol in the presence of a base in an organic solvent, or in a mixture of water with an organic solvent miscible or immiscible with water, to give the compound (I-B) having the following formula:



(I-B)

wherein R_1 and R_2 are as above defined;

b) nitration of the compound (I-B) in anhydrous conditions, in an inert organic solvent, by a mixture formed by steaming nitric acid with an inorganic acid different from nitric acid, or with an organic acid, or with an anhydride of one or two organic acids to give the nitroxy derivative of formula (I).

c) recovery of the final product by adding water to the organic phase, separating the phases, drying and

evaporating the organic phase.

2. A process according to claim 1, wherein in step a) the base is an inorganic or organic base.

3. A process according to claims 1-2, wherein in step a) the organic solvents are C_1-C_4 aliphatic alcohols; aromatic hydrocarbons, aliphatic esters, chlorinated organic solvents, alipahtic and cycloaliphatic ketones.

4. A process according to claims from 1 to 3, wherein in step a) the reaction is carried out at a temperature in the range -20°C and +50°C by using, with respect to the hydroxybenzylalcohol moles under reaction, an amount by moles respectively of acid halide (I-A) in the range between 1 and 2, preferably between 1.2 and 1.5 and an amount by moles of base in the range between 0.1 and 2, preferably between 0.5 and 2.

5. A process according to claim 1, wherein in step b) nitration is carried out at a temperature in the range -20°C and +40°C and the amount by moles of nitric acid is in a ratio between 1 and 6, preferably between 1 and 3, with respect to the moles of the compound (I-B), the amount by moles of inorganic acid different from nitric acid, or of organic acid or of organic anhydride as above defined, is in a ratio comprised beteen 0.5 and 6, preferably between 1 and 3 with respect to the moles of the compound (I-B).

6. A process according to claim 5, wherein nitration is carried out in the presence of an anhydride, which is premixed with the hydroxyester (I-B) and the resulting mixture added to the nitric acid solution in the inert organic solvent.

7. A process according to claim 6, wherein anhydride is acetic anhydride.

Docket No. ________________

ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
Nikaido, Marmelstein, Murray & Oram Intellectual Property Group

Declaration For U.S. Patent Application

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled
(Insert Title) "A PROCESS FOR OBTAINING (NITROXYMETHYL)PHENYL ESTERS OF SALICYLIC ACID DERIVATIVES"
the specification of which is attached hereto unless the following box is checked:

☐ was filed on June 21, 2000 As PCT International Application
Number PCT/EP00/05722 and was amended on ________

And/or was filed on ________ As United States Application
Number ________ and was amended on ________ .

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56.
I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International Application having a filing date before that of the application(s) for which priority is claimed:

(List prior foreign applications)	(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed
	MI99A001517	ITALY	9 JULY 1999	☒ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)

☐ See attached list for additional prior foreign or provisional applications.

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or §365(c) of any PCT International application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) (U.S. or PCT) in the manner provided by the first paragraph of 35, U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(List prior U.S. Applications or PCT International applications designating the U.S.)	(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

And I hereby appoint the firm of Arent Fox, Customer Number 004372 including as principal attorneys: Robert B. Murray, Reg. No. 22,980; Charles M. Marmelstein, Reg. No. 25,895; George E. Oram, Jr., Reg. No. 27,931; Douglas H. Goldhush, Reg. No. 33,125; David T. Nikaido, Reg. No. 22,663; Richard J. Berman, Reg. No. 39,107; Murat Ozgu, Reg. No. 44,275; Robert K. Carpenter, Reg. No. 34,794; Gregory B. Kang, Reg. No. 45,273; Rustan Hill, Reg. No. 37,351; Kevin Turner, Reg. No. 43,437; Carl Schaukowitch, Reg. No. 29,211; Hans J. Crosby, Reg. No. 44,634, and Brian A. Tollefson, Reg. No. 46,338.

Please direct all communications to the following address:
ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
1050 Connecticut Avenue, N.W., Suite 600
Washington, D.C. 20036-5339
Telephone No. (202) 857-6000; Facsimile No. (202) 638-4810

The undersigned hereby authorizes the U.S. attorneys named herein to accept and follow instructions from the undersigned's assignee, if any, and/or, if the undersigned is not a resident of the United States, the undersigned's domestic attorney, patent attorney or patent agent, as to any action to be take in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and the undersigned. In the event of a change in the person(s) from whom instructions may be taken, the U.S. attorneys named herein will be so notified by the undersigned.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Full name of sole or first inventor: Graziano CASTALDI

Inventor's signature: [signature] Date: November 08, 2001

Residence: BRIONA, Novara, Italy ITY

Citizenship: Italian

Post Office Address: Via Livia Gallina 5 - 28072 BRIONA, Novara, Italy

200

Full name of sole or second inventor: Erminio OLDANI

Inventor's signature: [signature] Date: November 08, 2001

Residence: CORNAREDO, Milano, Italy ITY

Citizenship: Italian

Post Office Address: Via Favaglie 41 - 20010 CORNAREDO, Milano, Italy

300

Full name of sole or third inventor: Gabriele RAZZETTI

Inventor's signature: [signature] Date: November 08, 2001

Residence: SESTO S. GIOVANNI, Milano, Italy ITY

Citizenship: Italian

Post Office Address: Via G. Puccini 60 - 20099 SESTO S. GIOVANNI, Milano, Italy

400

Full name of sole or fourth inventor: Francesca BENEDINI

Inventor's signature: [signature] Date: 08/11/2001

Residence: MILANO, Italy ITY

Citizenship: Italian

Post Office Address: Via Padova 286 - 20100 MILANO, Italy

Full name of sole or fifth inventor: _____

Inventor's signature: _____ Date: _____

Residence: _____

Citizenship: _____

Post Office Address: _____

Full name of sole or sixth inventor: _____

Inventor's signature: _____ Date: _____

Residence: _____

Citizenship: _____

Post Office Address: _____